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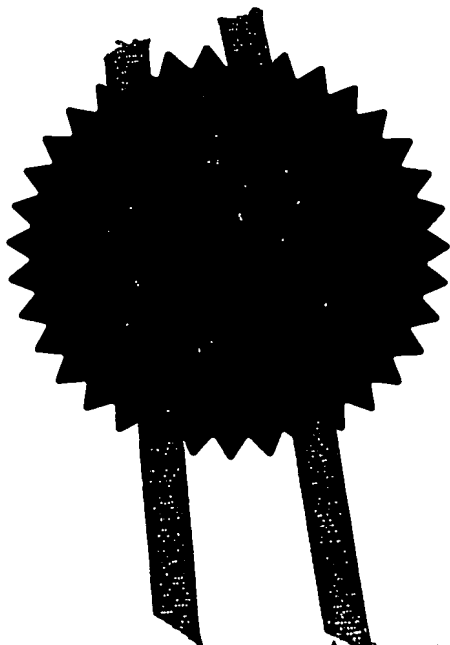
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Dated

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21 April 2004

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055EP03 E835105-1 D02898
P01/7700 0.00-0320740.4
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

J2071(C)/ps

2. Patent application number

(The Patent Office will fill this part in)

0320740.4

- 4 SEP 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

UNILEVER PLC
UNILEVER HOUSE, BLACKFRIARS
LONDON, EC4P 4BQ

Patents ADP number (if you know it)

50426956002

16 28002

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

4. Title of the invention

COMPOSITION FOR TOPICAL APPLICATION

5. Name of your agent (if you have one)

ELLIOTT, Peter William

"Address for Service" in the United Kingdom to which all correspondence should be sent (including the postcode)

PATENT DEPARTMENT, UNILEVER PLC
COLWORTH HOUSE, SHARNBROOK
BEDFORD, MK44 1LQ

Patents ADP number (if you know it)

16 28003

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

| Country | Priority application number (if you know it) | Date of filing (day / month / year) |
|---------|---|--|
| INDIA | 568/MUM/03 | 3 Jun 2003 |

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

| Number of earlier application | Date of filing (day / month / year) |
|-------------------------------|--|
| | |

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Answer YES if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

YES

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form

Description 11

Claim(s) 2

Abstract

see minutes

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77) 1

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature(s)

[Signature]

Date: 03/09/03

Sandra Jane EDWARDS, Authorised Signatory

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

Petra Silverstone (01234) 222893
petra.silverstone@unilever.com

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Notes

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COMPOSITION FOR TOPICAL APPLICATION

Technical Field of the Invention

The present invention relates to an improved cosmetic
5 composition for topical application to human skin to provide
enhanced protection from sunlight. The invention
particularly relates to a skin lightening composition
prepared from natural actives.

10 Background and Prior Art

Melanin is the black pigment synthesised by the action of the
enzyme tyrosinase on the amino acid tyrosine. The reaction
takes place in organelles called melanosomes contained within
cells called melanocytes. Melanocytes transfer melanosomes
15 with melanin to neighbouring keratinocytes which harbour
these organelles till they are themselves shed from the body
from the superficial layers of the skin. The intensity of
the skin colour is directly related to the number, the size,
melanin content, the rate of formation and transfer of
20 melanosomes to keratinocytes and degradation of melanin in
keratinocytes. Melanin is also an important protectant of
skin and tissues beneath the skin as it has the capacity to
absorb incident ultraviolet light.

The UV range is divided into three regions, UV-A, having a
25 wavelength of from about 320 to 400 nm which gives a tanning
effect without inflammation; UV-B, having a wavelength of
from about 290-320 nm which is responsible for erythema
(sunburn) and eventually for tanning; and UV-C, having a
wavelength of from about 200-290 nm, normally absorbed by the
30 ozone layer in the earth's atmosphere, but which is
potentially very damaging to the skin.

Melanogenesis and pigmentation of the skin are closely related responses to irradiation by UV light. Exposure to sunlight leads to darkening of the skin by immediate pigment darkening of already formed melanin, and also by formation of new melanin. Many skin compositions are formulated for the purpose of maintaining the colour of the skin against darkening following exposure to ultra-violet light. These compositions have been based on materials which deflect and scatter incident ultra-violet light of the wavelength which produce burning and tanning of the skin or which absorb this light.

Conventional skin lightening compositions are based on sunscreens or skin lightening agents. The latter are believed to control dispersion of melanosomes or inhibit tyrosinase. Sunscreens alone can not lighten the skin beyond the natural skin colour and their only action is to reduce the ingress of ambient ultraviolet radiation into the skin. Thus, they exert their effect only during the day. Some of the compounds used as skin lightening agents are also known to have undesirable side effects.

Several cosmetic products formulated using plant parts are available in the market. The advantages of plant source of actives in various cosmetic preparations such as skin creams, shampoos, hair applications, perfumes, soothing and nourishing creams etc has been well established. Synthetic actives are considered to be harsher than similar actives obtained from natural sources such as plants.

US20030096023 discloses tyrosinase inhibitors obtained from several dicotyledonous plant species thus leading to skin lightening. The plants are those belonging to the family Polygonaceae, Rosaceae, and Onagraceae.

5

The present inventors have identified that plant extracts of the species belonging to the genera *Symplocos* or *Rubia* on topical application to the skin give improved skin lightening benefits. It is possible to formulate cosmetic compositions incorporating the extracts from these plants to provide protection from the UV damage caused by the sun's radiation and also bring about lightening of the skin.

10

JP2001192317 (Shiseido) 2001, discloses matrix metalloproteinases inhibitors from several plants including *Symplocos*. Such an inhibition provides benefit in preventing wrinkles, skin aging.

15

US6258344 (Procter, 2001), discloses skin lightening compositions having certain hydroquinone derivatives, and lists *Rubia* under the class of natural anti-inflammatory agents.

20

JP09175962 (Lion, 1997), discloses use of plants belonging to the family of *Rubia cordifolia*, in a hair dyeing composition. This refers to darkening of hair which is contrary to the skin lightening effect.

25

JP2001163755 (Shiseido, 2001), discloses the use of *Glycyrrhiza* in preparations for external use for skin to

30

obtain skin bleaching effect and JP11021228 (Kanebo, 1999) discloses *Glycyrrhiza* as an anti-inflammatory agent.

US6455057 (Elizabeth Arden, 2002), discloses a skin care composition comprising petroselinic acid and/or derivatives thereof; a phenolic compound and/or mixtures thereof; and a dermatologically acceptable vehicle for treating wrinkles and soothing sensitive skin. However, they disclose coriander seed oil as a source of petroselinic acid.

However, none of the prior art teaches the skin lightening and protection against damaging effects of ultraviolet radiation by using the extracts of *Symplocos* or *Rubia* and cosmetic compositions comprising them.

It is the object of the invention to provide a synergistic cosmetic composition comprising skin lightening actives selected from plant sources.

It is another object of the invention to provide a synergistic cosmetic composition that will provide protection against the damaging effects of ultra violet radiation by the use of actives from natural sources.

It is yet another object of the invention to provide a synergistic cosmetic composition that will provide skin lightening with out requiring the use of chemical actives.

Summary of the Invention:

According to the present invention there is provided a cosmetic skin lightening composition comprising an extract of the plant *Symplocos* or *Rubia* or a mixture thereof.

According to the preferred aspect of the present invention there is provided a cosmetic skin lightening composition comprising 0.1-50% by weight of the composition an extract of the plant *Symplocos* or *Rubia* or a mixture thereof.

5

According to the preferred aspect of the present invention there is provided a cosmetic skin lightening composition comprising:

- i. 0.1-50% by weight of the composition an extract of the
10 plant *Symplocos* or *Rubia* or a mixture thereof;
- ii. 0.1 to 10% by weight of a sunscreen.

The plant parts used in the composition may be selected from any part of the plant but preferably from the stem, bark,
15 leaves, flowers, or roots. It is particularly preferred that the bark of the plant is used.

The extract is prepared using any suitable solvent and particularly preferred solvent is water.

20

Detailed Description of the Invention:

It is an essential aspect of the present invention that the plant extracts of *Symplocos* or *Rubia* are incorporated in the cosmetic composition. However, other plant extracts from
25 *Glycyrrhiza*, *Coriandum*, *Acorus* and useful conventional ingredients may be added to the composition.

Symplocos, is a genus belonging to the family *Symplocaceae*, commonly available in India. It has several species of which
30 *S. recemosa*, *S. paniculata* and *S. cochinchinensis* are the preferred species for use in the composition.

Rubia, is a genus belonging to the family Rubiaceae of which *R. cordifolia*, commonly available in India is the preferred species.

- 5 The conventional ingredients may be in the nature of sunscreens, other skin lightening agents chosen from natural or other synthetic sources, moisturizers, humectants, benefit agents, perfumes etc.
- 10 The composition of the invention may optionally comprise from 0.1 to 10%, preferably 0.5 to 5% by weight of one or more skin whitening agents. The skin whitening agent is preferably chosen from niacin, niacinamide or a precursor thereof that is capable of releasing niacinamide on the skin.
- 15 Niacinamide is the amide of niacin and is also known as nicotinamide or pyridine-3-carboxylic acid. An example of a compound which is a niacinamide precursor is niacinamide ascorbate. Other suitable skin whitening agents include extracts of placenta, hydroquinone and derivatives (eg.
- 20 arbutin), kojic acid, dicarboxylic acids (azelaic acid, sebacic acid), represented by the formula $\text{HOOC}-(\text{C}_x\text{H}_y)-\text{COOH}$ where $x=4$ to 20 and $y=6$ to 40, ascorbic acid and derivatives thereof, hydroxy acids (lactic acid, glycolic acid, malic acid, tartaric acid etc), ferulic acid, retinol and
- 25 derivatives or any other known skin whitening compounds.

The sunscreens used may be organic or inorganic in nature and are preferably chosen from 4-tertiary butyl-4'-methoxy dibenzoylemethane, available under the trade name PARSOL 1789

30 ex Givaudan, 2-ethyl hexyl methoxy cinnamate, available under the trade name PARSOL MCX ex Givaudan or mixtures of the two

5 sunscreen compounds. The composition comprises 0.1 to 10% by weight of the composition and preferably 0.1 to 5% by weight of the composition of a sunscreen compound. Inorganic sunscreens are for e.g. titanium dioxide, zinc oxide, and preferably in the micronized form.

10 The vehicle which forms part of the cosmetic composition is one or more substances which are mutually compatible with the sunscreen and if present, the skin whitening agent, and does not harm the skin. The vehicle can act as a diluent, dispersant or carrier for the other ingredients of the composition, and is therefore intended to ensure that they can be readily applied to and distributed evenly over the skin at an appropriate concentration.

15

The vehicles that can be used in compositions according to the invention can include water, powder absorbents, binders and carriers and liquids such as emollients, propellants, solvents, humectants and thickeners.

20

25 Examples of moisturisers and humectants include polyols, glycerol, cetyl alcohol, carbopol 934, ethoxylated castor oil, paraffin oils, lanolin and its derivatives. Silicone compounds such as silicone surfactants like DC3225C (Dow Corning) and/or silicone emollients, silicone oil (DC-200 Ex-Dow Corning) may also be included.

30 Compositions according to the invention can be prepared for topical application to the skin in the form of conventional product types such as creams, lotions, ointments and aerosol products.

The invention will now be illustrated by way of Examples. The Examples are for illustration only and do not in any way restrict the scope of the invention.

5 **Examples:**

In order to test the efficacy of an active in vitro three different cell based assays were used. The herb extract was used as the active that was prepared by the following procedure.

10

Herbs tested:

The barks of *Rubia cordifolia* (A), and *Symplocos racemosa* (B), were used in the different tests mentioned below.

15 Extraction procedure of herbs:

A 12.5% weight/Volume extract of the herbs was prepared in water. This extract was centrifuged at 14,000 x g for 10 min, filtered through a 0.2 micron filter, and 20 micro liter of stock/ml of cell culture media (=0.25% w/v) was used for all the cell culture assays.

i. In vitro synthesis of melanin:

The effect of the active on melanin synthesis was tested using melanocytes in culture. B16 melanocytes were grown in culture till they were about 60-70% confluent. The active was then added to the media and the cells were grown till they were confluent. The cells were then harvested and their melanin content was measured at 400 nm using a spectrophotometer. The effect of the actives are presented as a percent of the melanin content of control cells (where the active was not provided) in Table 1.

Table 1

| Treatment | Melanin Content (% of control) |
|-----------|--------------------------------|
| | Mean \pm SEM |
| A | 131.5 |
| B | 89.1 |
| A + B | 95.1 |

5 The data show that *Rubia* does not have an influence on the amount of melanin formed while *Symplocos* reduces the amount of melanin formed. A combination of *Rubia* and *Symplocos* show a synergistic reduction in the amount of melanin formed.

10 ii. Melanin uptake by keratinocytes:

The effects of the active on melanin uptake by keratinocytes were tested using HaCaT keratinocytes in culture. HaCaT keratinocytes were cultured till they reached confluence. Cells were then switched to media with no serum and 25 micro
15 gram of synthetic melanin was added to the cells along with the actives. After an overnight incubation, cells were washed and melanin content was measured using a spectrophotometer. The effect of the actives is presented as a percent of the melanin content of control cells in
20 Table 2.

Table 2

| Treatment | Melanin uptake (% of control) |
|-----------|-------------------------------|
| | Mean \pm SEM |
| A | 94.6 |
| B | 89.78 |
| A + B | 89.6 |

The data show that both *Rubia* and *Symplocos* alone and in
5 combination decreased the melanin uptake.

iii. Effect on skin lightening on a human panel:

Combinations of herbs comprising *Rubia cordifolia* and
Symplocos racemosa were formulated into cosmetic creams whose
10 formulation is presented in table 3 and tested on human
volunteers in a short-term skin lightening clinical.

Untreated and Placebo cream without the herbal extract were
maintained for comparison and the results on skin lightening
are presented in table 4.

15

Specific sites were marked on the forearms of 15 volunteers
for cream application. The initial skin colour reading on
each site served as untreated control. Study personnel
applied 3 mg of cream on to each test site. This process was
20 repeated for a period of 10 days. On the 11th day, the
subjects were clinically evaluated and scored on a colour
scale of 1 to 10 where 1 is the lightest and 10 is the
darkest. The data presented in table 4 is the difference in
skin colour before and after treatment.

25

Table 3

| Ingredients | % w/w |
|---------------------|--------|
| Glycerin | 1.0 |
| Potassium Hydroxide | 0.57 |
| Herbal extract | 30.0 |
| Stearic acid | 10.0 |
| Cetyl Alcohol | 0.6 |
| Preservatives | 0.3 |
| Silicon Oil | 0.5 |
| Water | To 100 |

Table 4

| Treatment | Skin lightening |
|---------------|-----------------|
| Untreated | 0 |
| Placebo cream | 0.29 |
| Herbal cream | 0.39 |

- 5 The data show that the herbal extracts even when formulated into a cosmetic composition showed significant skin lightening benefits.

10 Thus it is apparent from the above that it has been possible to formulate cosmetic compositions using extracts from plants to provide significant skin lightening benefits.

CLAIMS

1. A cosmetic skin lightening composition, comprising 0.1 -
50 % by weight of an extract plants from the families of
5 *Symplocos*, *Rubia* or a mixture thereof.
2. The cosmetic skin lightening composition of claim 1,
additionally comprising 0.1 - 10 % by weight of a
sunscreen.
- 10 3. The cosmetic skin lightening composition claim 1 or claim
2, further comprising 0.1 - 10 % by weight of one or more
skin whitening agents.
- 15 4. The cosmetic skin lightening composition of any preceding
claim, wherein the extract of *Symplocos* and/or *Rubia* is
selected from *Symplocos recemosa*, *Symplocos paniculata*,
Symplocos cochinchinensis, *Rubia cordifolia* or mixtures
thereof.
- 20 5. The cosmetic skin lightening composition of any of claims
2 to 4, wherein the sunscreen is selected from 4-tertiary
butyl-4'-methoxy dibenzoylemethane, 2-ethyl hexyl methoxy
cinnamate, micronized titanium dioxide, or micronized
25 zinc oxide.
6. The cosmetic skin lightening composition of any of claims
3 to 5, wherein the skin whitening agent is niacin,
niacinamide or a precursor thereof.

7. The cosmetic skin lightening composition of any preceding claim further comprising extracts of *Glycyrrhiza*, *Coriandrum*, *Acorus* or mixtures thereof.
- 5 8. The cosmetic skin lightening composition of any preceding claim wherein the *Symplocos* or *Rubia* is extracted from the bark of the plant.

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Att

